Stroke prevention in clinical practice for primary care physicians

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Summary

Stroke is a leading cause of death and a major source of disability. Prevention of recurrent or first-ever stroke is the most desirable approach, and one in which primary care physicians can play a major role. Effective stroke prevention can also minimise the occurrence of fatal and non-fatal cardiovascular events. The three main strategies of primary and secondary stroke prevention are identification plus appropriate management of the major modifiable risk factors, consideration of suitable antithrombotic therapy, and revascularisation of symptomatic extracranial carotid artery stenosis. The major modifiable risk factors are hypertension, hypercholesterolaemia, diabetes mellitus, atrial fibrillation, cigarette smoking, and extracranial carotid artery stenosis. The overall management must be individualised, bearing in mind the important pathogenic mechanisms operating in an individual along with the contraindications to antithrombotic therapy or revascularisation procedures.

摘要

中風是頭號殺手，也是致殘的重要原因。無論是首次中風或是復發，預防都是最理想的治療方法，而當中基層醫生可以擔當重要的角色。有效預防中風可以減低其他致命和非致命性的心血管疾病。預防首次和復發中風的三大策略是確定和適當地治療可改變的高危因素；考慮適當的抗血栓塞治療；貫通有症狀的顱外頸動脈閉塞。主要可改變的高危因素包括：高血壓、高膽固醇血症、糖尿病、心房纖顫、吸煙和顱外頸動脈閉塞。製定整體治療方案要因人而異，針對病人的病理機制，同時也要考慮有無抗血栓治療和貫通血管手術的禁忌。

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Introduction

Stroke is the second leading cause of death in China and the third in Hong Kong; a major reason for hospital admission, and an important source of disability.[1,2] Ischaemic stroke accounts for about 80% of cases, intracerebral haemorrhage for about 20%, and subarachnoid haemorrhage <5%.[2,3] Cerebral venous sinus thrombosis and spinal cord strokes are rare.[4] In highly selected cases, intravenous thrombolysis using recombinant tissue plasminogen activator given within 3 hours of onset, acute defibrinogenation using intravenous modified viper venom given within 3 hours of onset, and intra-arterial thrombolysis using prourokinase given within 6 hours of onset are effective therapies for acute ischaemic stroke.[2] Unfortunately, acute thrombolysis or defibrinogenation is applicable only in <5% of stroke patients, and symptomatic haemorrhagic transformation of the acute infarct remains a major concern.[2]

About 15 to 20% of ischaemic strokes are preceded by a transient ischaemic attack (TIA), in which the symptoms subside quickly within 1 hour. Following a stroke or TIA, the patient may have recurrent stroke and/or other cardiovascular events. The term "risk factor" was first implied by the earliest report of the Framingham Study in 1961. Risk factors for stroke are associated with a higher incidence of first-ever or recurrent stroke; many are modifiable, but others are not (**Table 1**).[5] Uncommon or emerging risk factors include hyperhomocysteinaemia, hypercoagulable states, cerebral amyloid angiopathy, elevated C-reactive protein level, and sleep apnoea.[6] Depending on the presumed mechanism of the TIA or stroke, some risk factors may play a causal role (**Table 2**).[5] Most importantly, clinical trials have confirmed the benefit of appropriate management of the major modifiable risk factors for first-ever and recurrent stroke, the efficacy of suitable antithrombotic therapy, and the role of revascularisation of carotid artery stenosis. Thus, prevention of first-ever (i.e. primary prevention) or recurrent (i.e. secondary prevention) stroke is the most

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Table 1: Risk factors for major types of stroke[5]

Category	*Ischaemic stroke*	*Intracerebral haemorrhage*	*Subarachnoid haemorrhage*
Modifiable	Arterial hypertension Hypercholesterolaemia Diabetes mellitus Smoking Cardiac diseases Atrial fibrillation Carotid artery stenosis Peripheral artery disease Obesity Physical inactivity Alcohol abuse	Arterial hypertension Anticoagulation Acute thrombolysis Alcohol abuse Drug abuse	Intracranial saccular aneurysm Arterial hypertension Smoking Alcohol abuse Drug abuse
Non-modifiable	Advancing age Male gender Intracranial artery stenosis Ethnicity Family history Inherited diseases History of stroke/TIA Silent cerebral infarcts	Advancing age Ethnicity Inherited diseases Cavernoma	Advancing age Female gender Ethnicity Inherited diseases

desirable approach and probably the most cost-efficient way of reducing the medical and societal burden of stroke.[7] Effective stroke prevention is also beneficial in reducing the occurrence and severity of fatal and non-fatal cardiovascular events.

Major modifiable risk factors

Hypertension

Hypertension affects small arteries and arterioles, promotes microangiopathy, and leads to lacunar infarcts, subcortical arteriosclerotic encephalopathy or infarcts, or intracerebral haemorrhage. Hypertension also leads to macroangiopathy via acceleration of atherosclerosis in large and medium-sized arteries. In addition, it provokes hypertensive and ischaemic cardiac diseases and atrial fibrillation.

A recent meta-analysis of 61 prospective observational studies involving nearly one million individuals has shown a strong association between usual blood pressure (BP) and death from stroke, ischaemic heart disease or other vascular causes, without a threshold down to at least 115 mmHg systolic BP (SBP) and 75 mmHg diastolic BP (DBP).[8] Each difference of 20 mmHg SBP (or 10 mmHg DBP) is associated with a twofold difference in vascular-related mortality. These associations are similar for men and women and for ischaemic and haemorrhagic strokes.

Non-pharmacological lifestyle strategies are effective in reduction of BP.[6] Aerobic exercise reduces body weight as well as SBP by about 5 mmHg and DBP by about 3 mmHg. Weight reduction by 3 to 9% in obese hypertensive people may lower SBP and DBP by 3 mmHg. A similar benefit can be achieved by one of the following dietary changes: eating a diet rich in fruits and vegetables, salt restriction (of about 7g/day), potassium supplementation (of about 2g/day), and fish oil supplementation (of about 3g/day).

Regarding antihypertensive therapy in primary prevention, a meta-analysis of 17 trials involving more than 47,000 patients treated for about 5 years using regimens based mainly on diuretics or β-blockers has found that a reduction of 5 to 6 mmHg in DBP or of 10 to 12 mmHg in SBP will confer a 38% relative reduction in the incidence of both fatal and non-fatal strokes. The annual absolute risk reduction is 0.4% per year, but the magnitude of risk reduction depends on the basal risk of the hypertensive population.[9,10]

Regarding antihypertensive therapy in secondary prevention after TIA or stroke, a meta-analysis of 10 trials suggests that a lowering of 5 to 6 mmHg in DBP and of

Table 2: Pathogenic mechanisms of stroke and causal risk factors[5]

Ischaemic stroke	*Causal risk factor*
Large vessel atherosclerosis (macroangiopathy): large artery thrombosis, artery-to-artery embolisation, haemodynamic stroke	Hypertension, diabetes mellitus, hypercholesterolaemia, extra- or intracranial cerebral artery stenosis
Cardioembolism: embolic stroke	Atrial fibrillation, valvular disease, prosthetic valves, recent myocardial infarction, low ejection fraction
Small vessel arteriolosclerosis (microangiopathy): lacunar stroke	Hypertension, diabetes mellitus
Uncommon mechanisms	Dissection, vasculitis, hypercoagulability, migrainous stroke, vasospasm
Intracerebral haemorrhage	***Causal risk factor***
Hypertensive arteriopathy: deep, lobar, brainstem, or cerebellar	Hypertension
Cerebral amyloid angiopathy: lobar, recurrent	Cerebral amyloid angiopathy
Vascular malformations: parenchymal	Arteriovenous malformation, cavernomas
Bleeding tendency: lobar, cerebellar, multiple	Anticoagulation, thrombolysis, leukaemia, tumours
Uncommon mechanisms	Drug abuse, vasculitis
Subarachnoid haemorrhage	***Causal risk factor***
Common underlying lesion	Intracranial saccular aneurysms
Uncommon mechanisms	Arteriovenous malformations, cerebral amyloid angiopathy

10 to 12 mmHg in SBP for 2 to 3 years, or of 9 mmHg in SBP and 4 mmHg in DBP for 4 years, reduces the relative risk of stroke by about 28%.[11,12] A preliminary report from China indicates a relative reduction by 29% for a 2 mmHg reduction in DBP for 2 years.[13]

As hypertension typically has no obvious symptoms, primary care physicians should include BP measurement as part of their routine, irrespective of the presenting complaint. If the SBP and/or DBP are high, more frequent BP measurements should be obtained and the patient should be encouraged to take home BP readings. Adoption of a healthy lifestyle is important, and antihypertensive medication should be commenced when needed to achieve a SBP $\leq$130 mmHg and a DBP $\leq$80 mmHg or the lowest BP tolerated by the patient. Two cautions must be noted. First, abrupt reduction in BP after a recent stroke or TIA is discouraged. Second, patients at very old age or with severe bilateral carotid stenosis may not tolerate aggressive lowering of BP.

Results of the Heart Outcomes Prevention Evaluation Trial suggest that the addition of ramipril at 10 mg/day to the best medical therapy can reduce the relative risk of recurrent stroke, myocardial infarction and vascular deaths by 22% and the absolute risk by 1%.[14] However the class benefit of angiotensin-converting enzyme inhibitors (ACEI) remains controversial. Low-dose diuretics, low-dose β-blockers, calcium channel blockers, and ACEI are similarly effective, provided that adequate reduction in BP is achieved.[9-16] Drug cost, side effects, and other associated medical conditions, such as diabetes mellitus, ischaemic heart disease, left ventricular hypertrophy and renal impairment, influence our choice of antihypertensive agents as single or combination therapy.

Hypercholesterolaemia

High levels of LDL cholesterol and low levels of HDL cholesterol promote atherosclerosis and coronary artery disease. Lipoprotein (a) resembles LDL in structure. Lipoprotein (a) is increased in stroke patients, but a causal relationship is not established.[17] Elevated triglyceride levels increase the risk of coronary artery disease and peripheral arterial disease. Elevated triglyceride levels are often seen in the metabolic syndrome with central obesity, insulin resistance, low levels of HDL cholesterol and hypertension.[18] Although triglycerides play a role in atherogenesis, an independent association with stroke has not been confirmed.

Epidemiological studies, primarily designed to study coronary artery disease in middle-aged subjects with a relatively low stroke risk, do not support any association between plasma cholesterol level and all types of stroke combined.[19] In the Multiple Risk Factor Intervention Trial study of 350,000 middle-aged men, the risk of fatal non-haemorrhagic stroke was directly related to increasing cholesterol levels.[20]

Low serum cholesterol levels have been associated with haemorrhagic stroke, but the relationship is not yet clarified.[20] Cholesterol-lowering treatment with statins, gemfibrozil and niacin does not increase the risk of haemorrhagic stroke.

A meta-analysis of clinical trials involving about 39,000 patients at low risk of stroke has shown that using statins (β-hydroxymethylglutaryl coenzyme-A reductase inhibitors) to lower plasma cholesterol concentrations reduces the relative risk of stroke by about 25% and the absolute risk by about 0.17%.[21] Nevertheless, the benefit is mainly seen in patients with a history of coronary artery disease. The recommended level of LDL cholesterol is less than 3.4 mmol/L.[22]

In a total of more than 20,000 high risk individuals, simvastatin at 40 mg/day reduced the serum cholesterol level over 5 years by 1.0 mmol/L and achieved a relative reduction in stroke, myocardial infarction and vascular death by 24%. The relative reduction in stroke alone was 27%; there was a non-significant trend towards a small reduction in haemorrhagic stroke.[23] Among 3,000 patients with previous stroke, simvastatin treatment reduced the relative risk of all vascular events by about 20%.

Patients with stroke or TIA should have a complete lipid analysis. Treatment with lipid-lowering agents reduces the risk of stroke and other major vascular events. Elevated LDL cholesterol or the diabetic dyslipidaemic triad (elevated triglycerides, elevated small LDL particles and low levels of HDL cholesterol) are common in type II diabetics. Dietary and drug therapy should be used to achieve an LDL cholesterol level < 2.6 mmol/L in patients with overt atherosclerosis or diabetes mellitus.[22]

Diabetes mellitus

Diabetes mellitus is becoming more prevalent in both developed and developing countries. High body mass index and obesity are associated with hyperinsulinaemia, insulin resistance and type II diabetes mellitus. Hyperglycaemia harbours a prothrombotic state with endothelial dysfunction, increased platelet aggregation and adhesiveness, decreased fibrinolytic activity, and enhanced inflammation within atherosclerotic plaques.[24] Type II diabetics appear to be at a higher risk of fatal and non-fatal stroke than type I diabetics probably because type II diabetics typically have multiple risk factors. Diabetes mellitus promotes both macroangiopathy and microangiopathy.

In the Atherosclerotic Risk in Communities Study, type II diabetics with fasting glucose levels ≥7.8 mmol/L had a relative risk of 3.7 for stroke when compared to those with fasting glucose levels between 7.0 to 7.8 mmol/L.[25] The age-adjusted risk of diabetic versus non-diabetic women in the Nurses Health Study was 4.1, 5.0, and 3.8 for all strokes, fatal strokes, and non-fatal strokes, respectively. Diabetic stroke patients have double the risk of recurrent stroke.[26]

Tight glycaemic control via diet, sulphonylurea, metformin, and/or insulin reduces the risk of retinopathy, nephropathy, and neuropathy in patients with type I or II diabetes mellitus.[27,28] These are microvascular complications. The benefit of glycaemic control on macrovascular complications such as stroke is uncertain, but our goal is to achieve a near-normal fasting glucose level, a haemoglobin A1c level <7%, and satisfactory control of all other risk factors.

The incidence of diabetes mellitus increases with advancing age and obesity, and diabetes mellitus is often undiagnosed until the patient presents with stroke or other diabetic complications. Primary care physicians should enquire about diabetic symptoms and routinely test blood glucose whatever the presenting symptoms.

Atrial fibrillation

Atrial fibrillation is common: 1% of the general population, 6% of people >65 years old, and 10% of those >75 years old.[7] Atrial fibrillation causes ischaemic stroke via systemic embolisation of left atrial thrombi. As rheumatic heart disease is disappearing, non-valvular atrial fibrillation (NVAF) has become the most common cause of atrial fibrillation. Silent cerebral infarcts, often multiple and bilateral, are detected by computed tomography in 25% of patients with atrial fibrillation.[7]

Patients with atrial fibrillation have an increased risk of stroke (**Table 3**). Long-term anticoagulation (with warfarin) is the standard practice for secondary stroke prevention in patients with atrial fibrillation due to valvular heart disease or non-valvular causes.[29] For primary prevention, long-term anticoagulation may be considered in patients with one or more additional factors: >65 years old, hypertension, diabetes mellitus, recent heart failure, enlarged left atrium, or left ventricular dysfunction. However, patient's compliance with warfarin and follow up, availability of monitoring, and risk of bleeding must be considered.[7] Patients and their relatives should be given adequate information to minimise the risk of under- and over-anticoagulation. Low-intensity anticoagulation, with international normalised ratio (INR) between 2 and 3, carries a 1 to 2% annual risk of severe bleeding, including a 0.3% incidence of intracerebral haemorrhage.[7] Patients at low risk for cardioembolism and those with contraindications to warfarin should be given aspirin at low dose, which reduces stroke risk by 22%.[7]

Cigarette smoking

Cigarette smoking induces atherosclerosis and ischaemic heart disease. In addition, cigarette smoking increases blood levels of fibrinogen and other clotting factors, promotes platetet aggregation, elevates the haematocrit, reduces the level of HDL cholesterol, produces acute rises in arterial BP, and enhances the breakdown of elastic tissue within arteries.[7] The latter two effects may produce arterial rupture and intracerebral or subarachnoid haemorrhage. Observational studies reveal a fall in first-ever stroke risk when smokers quit smoking. The relative risk of stroke in smokers versus ex-smokers is 1.2, but the relative risk of ex-smokers versus non-smokers remains at 2.5 for 5 to 10 years after cessation.[6] The risk of stroke in previously light smokers (<20 cigarettes per day) becomes identical to that of non-smokers at 5 years after cessation, but the relative risk of previously heavy smokers versus non-smokers remains high at 2.2.[30] Observational studies suggest that cessation of smoking decreases the relative risk of recurrent stroke by about 33%.[6]

Carotid artery stenosis

Extracranial carotid artery stenosis is an important risk factor for symptomatic and silent stroke. The pathogenic mechanisms include thromboembolism and haemodynamic compromise. The risk for stroke is influenced by many factors: occurrence of symptoms, degree of stenosis, presence of ulceration, contralateral occlusion, presence of collaterals, number of other risk factors, and cerebral infarction on computed tomography of the brain.[7] Carotid artery stenosis is relatively common in Hong Kong Chinese with coronary artery disease.[31]

Carotid artery stenosis can be corrected by carotid endarterectomy or percutaneous transluminal angioplasty with or without stenting. The latter is a promising alternative awaiting evidence from randomised control trials. Carotid endarterectomy may carry a perioperative risk of morbidity and mortality of 5 to 7% or more.[32] A

Table 3: Indications for and effects of anticoagulation in preventing thromboembolism[29]

Indication and condition	*Thromboembolic rate*	*Risk reduction*
Prevention of systemic embolism		
Mechanical prosthetic heart valve	8.6% per year	4-8% per year
Bioprosthetic heart valve	5-6% in first 3 months	uncertain
Non-valvular atrial fibrillation	4.5% per year	3% per year
Recent myocardial infarction	1.2-2.6% per year	1-2% per year
Rheumatic mitral valve disease	8% per year	6% per year
Prevention of recurrent disease		
Ischaemic stroke in atrial fibrillation	12% per year	8% per year
Venous thromboembolism	22-29% in first 3 months	up to 22% per year

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perioperative risk of ≥10% will obviate any benefit of carotid endarterectomy. Patients with severe asymptomatic carotid artery stenosis have a 1.5 to 2% annual stroke rate.[7,32] Scientific data do not support a role of carotid endarterectomy in patients with asymptomatic carotid artery stenosis of any severity. Aspirin at low dose and modification of risk factors are recommended.

In contrast, patients with recent TIAs related to severe (70 to 99% by diameter) carotid artery stenosis have a 12 to 13% rate of stroke in the first year and a cumulative rate of 30 to 35% in five years, and those presenting with non-disabling strokes have a 5 to 9% annual rate of recurrence and a five-year rate of 25 to 45%.[32] Carotid endarterectomy reduces the annual risk of stroke to 2%. The benefit is less when the stenosis is between 50 and 70%. Surgery is inferior to best medical management if the symptomatic stenosis is <30%.[32]

Other modifiable risk factors

Physical inactivity is a well-established risk factor for coronary artery disease but not for stroke.[7] As physical activity is beneficial to hypertension, diabetes mellitus and obesity, regular moderate exercise for at least 30 minutes a day is recommended.[6]

Obesity doubles the risk of stroke.[6,7] It is associated with hyperglycaemia, hypertension, and hypercholesterolaemia. Abdominal obesity is more important than general obesity. Weight reduction is recommended in obese persons.

Light to moderate intake of alcohol (1 to 2 drinks per day) reduces the risk of coronary artery disease.[6,7] On the other hand, long-term heavy alcohol intake (5 or more drinks per day) or binge-drinking increases the risk of haemorrhagic and ischaemic stroke. Physicians should discourage heavy or binge drinking. There is no need to change the habit of no or light to moderate drinking.

Use of oral contraceptives with high oestrogen content (≥50 μg) increases the relative risk of all types of stroke by 3 times.[6,7] In contrast, use of those with low oestrogen content (<50 μg) does not increase the stroke risk. Presence of additional risk factors may further enhance the stroke risk. Progestogen-only pills might be an alternative.

Hormone replacement therapy has no benefit in stroke prevention.[6,7] There may be a slight increase in the stroke risk and/or the severity of stroke in patients taking hormone replacement therapy. It is not therefore advisable to recommend this treatment to patients with a history of stroke.

Migraine with aura and possibly migraine without aura is associated with a higher risk of stroke, although the absolute risk of stroke remains low.[6,7] Migraineurs should stop smoking and choose their contraceptive method carefully, especially when other risk factors are present.

Antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin antibodies and anti-β_2-glycoprotein I antibodies, are detected in 1 to 5% of young healthy volunteers and are much more common in patients with systemic lupus erythematosus.[6] Antiphospholipid syndrome refers to presence of these antibodies plus vascular thrombosis or certain complications of pregnancy. When stroke or TIA occurs, long-term anticoagulation is recommended.

Increased levels of homocysteine, an amino acid from methionine, are associated with an increased risk of ischaemic stroke.[6] Homocysteine may affect vascular smooth muscle or endothelium. Folic acid and vitamin B_{12} normalise elevated homocysteine levels. An on-going trial will clarify the value of this intervention in stroke prevention.

Antithrombotic therapy

Antiplatelet agents

Aspirin, dipyridamole, ticlopidine and clopidogrel are antiplatelet agents useful in stroke prevention among high-risk subjects. Aspirin, an irreversible inhibitor of the cyclooxygenase in the platelets, is efficacious in preventing first myocardial infarction but not first-ever ischaemic stroke.[33] Other antiplatelet agents have not been tested in primary stroke prevention. Aspirin is not recommended for primary prevention of stroke because of lack of benefit and a small increase in the risk of intracerebral haemorrhage.

Meta-analysis of data from clinical trials on antiplatelet agents in high risk individuals shows that aspirin reduces stroke risk by 31%.[34] The recommended

dosage is 80 to 300 mg daily. Higher doses cause more gastrointestinal side effects and may not be more effective.

Apart from cyclooxygenase, platelets can be activated via the ADP-receptor. Ticlopidine (250 mg once or twice daily) and its derivative, clopidogrel (75 mg daily), are irreversible antagonists of the ADP-receptor; they are more expensive than aspirin. A meta-analysis of four trials on ADP-receptor antagonists involving over 22,000 high-risk patients has shown that ADP-receptor antagonists are superior to aspirin with a relative risk reduction in serious vascular events of 10%.[35] Ticlopidine is not ulcerogenic but may cause troublesome side effects, including skin rash, leucopenia, aplastic anaemia and cholestatic jaundice. Clopidogrel is the safer alternative.

Use of instant release dipyridamole alone or in combination with aspirin does not reduce the risk of recurrent ischaemic stroke. Irregular gastrointestinal absorption and the short plasma half-life of dipyridamole may be the key factors. The Second European Stroke Prevention Study has shown that the combination of aspirin at 25 mg plus an extended release formulation of dipyridamole at 200 mg to be taken twice daily is more effective than aspirin alone in preventing all strokes, conferring an extra 22% relative risk reduction.[36] Mortality rate is not affected. Dipyridamole is a vasodilator, and about 8% of patients stop taking the combination because of headache. Risk of bleeding is the same as the group taking aspirin alone.

Glycoprotein IIb/IIIa inhibitors block the final pathway for platelet aggregation. Oral glycoprotein IIb/IIIa inhbitors significantly increase the bleeding risk and do not have a role in secondary stroke prevention.

It may be logical to combine antiplatelet agents with different mechanisms to achieve better effects. The combination of clopidogrel and aspirin has been shown to be superior to aspirin alone in patients with acute coronary syndrome.[37] Ongoing studies are comparing the benefit between clopidogrel plus aspirin and clopidogrel or aspirin alone.

Anticoagulation

The haemostatic system is composed of a highly regulated series of procoagulant and anticoagulant zymogens and cofactors. Haemostatic imbalance can lead to thrombosis or bleeding in the arterial or venous circulation. Anticoagulation is considered in patients at a high risk of cardioembolic stroke or venous thrombosis and in those with recurrent TIAs or minor stroke despite good control of risk factors plus use of antiplatelet agents (**Table 3**).[29]

Warfarin exerts its effects in the liver via inhibition of vitamin K-dependent factors (coagulation factors II, VII, IX and X, and proteins C, S and Z). It is highly protein-bound, has a half-life of 30 to 40 hours, requires long periods to reach stable anticoagulation levels, and still has effects for a long time after cessation.[29] Apart from genetic factors such as hepatic cytochrome P-450 polymorphism, intercurrent illness, diet, and concurrent drug therapy (**Table 4**) may affect the dose response. Dietary intake of foods rich in vitamin K should be kept uniform with the INR checked 1 week after initiation or termination of any medication known to interact with warfarin. INR ≥ 1.6 offers substantial protection against ischaemic stroke, maximal effect is achieved with INR between 2 and 3, and the risk of major haemorrhage is high with INR above 4. Warfarin is teratogenic and contraindicated in patients with a bleeding tendency, gait imbalance and falls, uncontrolled seizures, poor compliance, and lack of monitoring.[29]

Role of primary care physicians in stroke prevention

Primary care physicians can play a key role in stroke prevention. Regardless of the reasons for consultation, primary care physicians should detect and tightly control hypertension, hypercholesterolaemia, and diabetes mellitus. They should educate patients and their family members about risk factors and symptoms of cerebrovascular and cardiovascular diseases and encourage adoption of a healthy lifestyle via smoking cessation, weight reduction, moderation in drinking, regular physical exercise, and good drug compliance. Primary care physicians should recognise possible TIAs, minor strokes, and carotid bruits. When acute stroke is suspected, patients should be urgently referred to a nearby accident and emergency department. Where there is a history of recent TIA or strokes, primary care physicians are in a good position to confirm the nature of the cerebrovascular event, detect all risk factors, and supervise all secondary prevention measures.

Table 4: Common drugs that decrease or increase the effects of warfarin[29]

Decreased anticoagulation effect	*Increased anticoagulation effect*
Antacids	Alcohol
Antiepileptics: carbamazepine, barbiturates	Allopurinol
Antihistamines	Amiodarone
Antithyroid drugs	Anabolic steroids
Cholestyramine	Aspirin, acetaminophen
Garlic	Antibiotics: trimethoprim plus sulphamethoxazole, amoxicillin plus clavulanic acid, erythromycin, metronidazole, quinolones, isoniazid, cephalosporin, carbenicillin, high dose penicllins
Ginseng	
Griseofluvin	
Penicillins	
Rifampicin	
Sucralfate	
Vitamin K	Antifungal: ketoconazole, fluconazole
	Cimetidine
	Clofibrate
	Danshen (*Salvia miltiorrhiza*)
	Disulfiram
	Ginkgo
	Heparin
	Non-steroidal anti-inflammatory drugs
	Omeprazole
	Phenytoin
	Statins
	Sulfinpyrazone
	Thyroxine

Primary prevention

The goal is identification and tight control of the modifiable risk factors (**Table 1**). Except for the following, there is no evidence for any benefit from antithrombotic therapy or corrective procedure for extracranial carotid artery stenosis in reducing the risk of first-ever stroke.

Aspirin at low dose is recommended in high risk individuals, and it is effective in primary prevention of myocardial infarction. Long-term anticoagulation with an INR of about 2 should be considered in patients with chronic or paroxysmal atrial fibrillation plus an additional risk factor (**Table 3**). Chronic anticoagulation with an INR of about 3 should be maintained in patients with mechanical prosthetic heart valve. Anticoagulation is beneficial after recent transmural myocardial infarction and possibly also in patients with very low ejection fraction.

Secondary prevention

Risk of recurrent stroke is higher than first-ever stroke in people with otherwise identical risk factor profiles. Tight control of modifiable risk factors is recommended (**Table 1**). BP lowering should be initiated several days or a few weeks after acute stroke or TIA with normal values achieved over a couple of months. In acute ischaemic stroke, the BP should not be lowered unless the DBP is >120 mmHg or the SBP is >220 mmHg.[38] In acute intracerebral haemorrhage, mean arterial BP levels should be maintained just below 130 mmHg in patients with a history of hypertension.[39] Long-term BP reduction probably decreases stroke recurrence even in normotensive patients.

If cardioembolic mechanism is responsible for the TIA or ischaemic stroke, oral anticoagulation with an INR of 2 to 3 is recommended (**Table 3**). When cardioembolic stroke or TIA recurs despite adequate anticoagulation, the management is uncertain. Unproven options include an increase in INR and addition of an antiplatelet agent, but the risk of haemorrhage is also increased.

Patients not requiring anticoagulation should receive an antiplatelet agent unless there is a contraindication. The most commonly used agent is aspirin. Clopidogrel, a derivative of ticlopidine, is non-ulcerogenic and largely free from the side effects of ticlopidine; it is slightly more effective than aspirin. Owing to its high cost, clopidogrel is usually considered only if aspirin is not tolerated. The combination of aspirin and an extended release form of dipyridamole taken twice per day is superior to aspirin alone but is also more expensive than aspirin and so should be considered in patients at high risk of ischaemic stroke. Patients developing recurrent ischaemic events despite aspirin may be offered the combination or clopidogrel or aspirin plus clopidogrel.

Ultrasonography of the carotid artery is a good screening method for symptomatic severe carotid artery stenosis. Patients should be referred to a specialist for further workup and consideration of carotid endarterectomy. Percutaneous transluminal angioplasty with stenting is an emerging alternative.

Aggressive and chronic lowering of BP is the most important measure after intracerebral haemorrhage. Control of other risk factors is desirable, but antiplatelet agents or anticoagulation are not recommended. An

Key messages

1. Prevention of first-ever or recurrent stroke is the most desirable approach.
2. Stroke prevention can be achieved by: (1) identifying all risk factors and controlling the modifiable risk factors; (2) appropriate use of antithrombotic therapy; and (3) consideration of revascularising extracranial carotid artery stenosis.
3. Causal risk factors are different for different types and subtypes of strokes.
4. The major modifiable risk factors include hypertension, hypercholesterolaemia, diabetes mellitus, atrial fibrillation, smoking and extracranial carotid artery stenosis.
5. Antithrombotic therapy should be considered in people at risk for cerebral ischaemia. Antiplatelet therapy is effective in secondary prevention of atherothrombotic stroke. Anticoagulation prevents cardioembolic or venous stroke, but contraindications should be noted.

underlying arteriovenous malformation may require definitive treatment. Clipping or coiling the saccular aneurysm is highly effective in avoiding rebleeding after subarachnoid haemorrhage.

Conclusion

Primary care physicians are in a better position than specialists to identify all risk factors for stroke, promote a healthy life style and control modifiable risk factors. Antiplatelet therapy is indicated in secondary prevention of ischaemic stroke. Anticoagulation is indicated in cardioembolic stroke and venous thrombosis. Family physicians should be able to monitor long-term antiplatelet therapy or anticoagulation. Patients with recurrent strokes despite optimal secondary stroke prevention, patients in whom risk factors cannot be controlled, patients with no identifiable risk factor, and patients with symptomatic extracranial carotid artery stenosis should be referred to specialists.

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